REMARKS

The amendment to the paragraph beginning at page 25, line 4 amends the "DOCK" motif peptide sequences in line 8 and the motif labels in line 7. This is supported by the two motifs found in FIG. 3B. These amino acid motifs presently found on line 8, i.e., (P+EXAI+XM) and (LXMXL+GXVXXXVNXG), which are presented in FIG. 3B, boxes E and F, on the two lines labeled "CONSENSUS", appear as:

```
P+E AI+ M
        +
```

and

```
L M L+G V   VN G
  L     I,
```

respectively. The "+" symbol and the letters "L" and "I" on the second "CONSENSUS" line indicate optional amino acid variants at these indicated positions occur in ther homology comparison. Therefore, the terminal "M" residue in the first motif (motif E) has been amended to a "+" symbol to reflect these variants. The two positions in the second motif (motif F) have also indicated these optional amino acid variants by the "M/L" and "V/I" designations. The Sequence Listing has incorporated the indicated optional variants into their respective positions.

The amendment includes amending the letters to which those highly conserved non-tyrosine containing regions refer. The first amino acid motif is presented in FIG. 3B, page 1 of 2, where the last region boxed is labeled region E. This region is followed by a boxed region labeled "F" in FIG. 3B, page 2 of 2, instead of region "G" as designated on page 25, line 7.

This amendment further corrects the number of amino acid residues stated to be separating these two motif sequences in line 8. Although the number of amino acid residues between boxes E and F is stated to be nine on line 8 of the Specification, FIG. 3B does not illustrate the entire contiguous sequence of amino acids in the CLASP protein homologs. The actual number of amino acid residues appearing in the CLASP

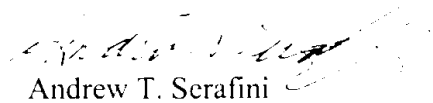
protein sequences corresponding to these motifs appears in FIG. 3A, where all contiguous residues are represented. In FIG 3A, page 5 of 5, the regions of homology surrounding the box labeled "Coiled-Coil 1" contain the corresponding regions labeled motifs E and F from FIG. 3B. These motifs extend from the "P" residue one amino acid to the left of the boxed "Coiled-Coil 1" in the top line of the homology groupings to seven amino acid residues into the second line of homology groupings, where the conserved "...VNXG" terminal portion of motif F occurs. By comparison of the E and F motifs with the sequences in FIG 3A, it can be seen that the actual number of residues separating these motifs is actually 20. Thus, no new matter has been introduced by the amendments to this paragraph.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-134, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 6 of page 6 has been amended as follows:

Figure 1. Preliminary CLASP-5 cDNA sequence (SEQ ID NO:3; amino acid sequences = SEQ ID NOS:4 and 5). Notable protein motifs are labeled above the nucleotide sequence.

Paragraph beginning at line 20 of page 6 has been amended as follows:

Figure 3. A. Amino acid sequence of human and rat CLASP proteins. Sequences were aligned using ClustalW. One letter amino acid abbreviation used. Protein motifs are found within the labeled boxes. -A -"-" indicates gaps that are placed to acquire a best overall alignment. Other abbreviations: "HC2A" Human CLASP-2 sequence (SEQ ID NO:9), "KIAA" KIAA1058 sequence (SEQ ID NO:10) (Genbank Accession No. AB028981), -"rat" TRG gene (SEQ ID NO:11) (Genbank Accession No. X68101), "HC4" -Human CLASP-4 sequence (SEQ ID NO:12), "HC1" Human CLASP-1 sequence (SEQ ID NO:13), "HC3" Human CLASP-3 sequence (SEQ ID NO:14), "HC5" Human CLASP-5 sequence (SEQ ID NO:15). **B.** Alignment of DOCK motifs found within the human CLASPs (SEQ ID NOS:16-20, 24, 25, 27-31, 35, 37-43, 47 and 49-55) and rat TRG (SEQ ID NOS:26, 36 and 48) and compared to canonical DOCK motifs (SEQ ID NOS:21-23, 32-34, 44-46 and 56-58). Consensus amino acids found within all DOCK motifs are also indicated.

Paragraph beginning at line 30 of page 6 has been amended as follows:

Figure 4. **A**. Nucleotide (SEQ ID NO:3) and predicted amino acid sequence (SEQ ID NO:4) of CLASP-5 cDNA. Notable protein motifs are indicated. Additionally, boundaries between exons and introns are indicated by arrows. These boundaries were defined by sequencing Bacterial Artificial Chromosomes containing genomic DNA corresponding to CLASP-5 (BACs). BACs were sequenced using primers derived from exon sequences corresponding to the CLASP-5 cDNA (SEQ ID NOS:59-63). Each exon/intron boundary is noted (as "Ref" with an appropriate reference number) above the cDNA sequence. The References contain exact nucleotide location of introns. The names and nucleotide numbers of the primers that were used in sequence reactions are also indicated. All nucleotide numbers refer to CLASP-5 cDNA sequence. As shown in the Reference, not all of the sequence from sequencing reactions produced sequence matching the cDNA. -These nucleotide sequences that did not match the exon sequence for CLASP-5 were considered to be intron sequences. **B**. Alignment of human (SEQ ID NOS:9, 10 and 12-15) and rat (SEQ ID NO:11) CLASP amino acid sequences by ClustalW. Notable protein motifs are indicated. Additionally, the exon/intron borders described in part A are indicated with hand-drawn vertical lines between appropriate amino acids. Reference numbers are indicted in the right margin and correspond to References in part A.

Paragraph beginning at line 10 of page 8 has been amended as follows:

Figure 7. Sequence of human CLASP-5 exons and introns, and promoter. **A)** Sequence of human CLASP-5 exons and intron borders (SEQ ID NOS:64-65). Sequence

template and Sequencher sequence analysis software. Due to the incompleteness of the Human Genome Project, only partial genomic sequence from human CLASP-5 was

obtained. 22 exons representing approximately -the 5' 40% of the human CLASP-5 cDNA sequence are presented in predicted 5' to 3' order. Exon sequences are underlined and are flanked by intron sequence. This exon/intron map could only have been produced having the isolated human CLASP-5 cDNA. Nucleotide numbers in parentheses refer to the exon sequence within the uniquely-generated, contiguous gi10045359 sequence, which is located **7B**. **B)** Ordered stretch of human genomic DNA at the CLASP-5 locus (SEQ ID NO:86) aligned from noncontiguous, shotgun sequencing from the Human Genome Project using the human CLASP-5 sequence from FIG. 6A to determine genomic DNA fragment order and orientation. **C)** ~~C)~~ Sequence of putative human CLASP-5 promoter (SEQ ID NO:87). The 5' terminus of the CLASP-5 cDNA is underlined. This sequence represents nucleotides 126774 to 128870 of Genbank entry gi10045359.

Paragraph beginning at line 27 of page 8 has been amended as follows:

Figure 8. Amino acid alignment and comparison between the human (h) CLASP family members (SEQ ID NO:88-93). Amino acid sequences were aligned using ClustalW. The alignment is presented in order of their greatest pairwise similarity scores. Single letter amino acid abbreviations are used. Astericks indicate complete identity, while colons and periods indicate sequence similarity among CLASP family members. Dashes indicate gaps inserted in the amino acid sequence to facilitate alignment. Labelled boxes are domains with similarity to known protein motifs; unlabelled boxes represent regions of similarity between all CLASPs and may represent CLASP-specific domains.

The CLASP-5 extracellular domain is characterized by one cadherin EC -like motif (Pigott, R. and Power, C., 1993, The Adhesion Molecule Factbook. Academic

Press, pg. 6; Jackson, R. M. and Russell, R. B., 2000, J. Mol. Biol. 296: 325-34). Several highly conserved cysteines are found in the extracellular domain, as well as various glycosylation signals. Through its extracellular domains, CLASP-5 may interact with ligands in a homotypic and/or heterotypic manner to establish the immunological synapse in conjunction with molecules such as TCR, MHC class I, MHC class II, CD3 complex and accessory molecules such as CD4, CD3, ICAM-1, LFA-1, and others. Many cadherins contain a pro-domain of approximately 50 to 150 amino acids that is removed before localization to the plasma membrane. This cleavage is presumed to be carried out by Furin (Posthaus, H. *et al.*, 1998, FEBS Let 438: 306-10) at a consensus sequence of RKQR (SEQ ID NO:6). Furin is a protease that is at least partially responsible for the maturation of certain cadherins. CLASP-5 contains the amino acid sequence RRTR (SEQ ID NO:7) encoded by the nucleotides 2770-2781. By homology, this region is around 924 amino acids into the predicted protein start site for hCLASP-5 cDNA indicated in FIG. 6.

Paragraph (**Table 1**) beginning at line 2 of page 24 has been amended as follows:

Table 1
CLASP-5 ITAM Motifs

Motif No.	Sequence Motif	SEQ ID NO:
1	YXXV-X_3-YXXV	8
2	YXXV-	-

Paragraph beginning at line 4 of page 25 has been amended as follows:

CLASP-5 polypeptides contain a new "DOCK" motif, not previously

There are also two highly conserved non-tyrosine containing regions (E and E-6) separated by 20 ~~nine~~ amino acids (P-EXAI-X-; SEQ ID NO:131) ~~(P-EXAI-XM)~~ and

(LX(M/L)XL+GX(V/I)XXXVNXG; SEQ ID NO:132) ~~(LXMXL+GXVXXXVNXG)~~
(where X is any amino acid).

Paragraph beginning at line 9 of page 52 has been amended as follows:

In one embodiment, the antisense sequence is complementary to relatively accessible sequences of the CLASP-5 mRNA (*e.g.*, relatively devoid of secondary structure). _This can be determined by analyzing predicted RNA secondary structures using, for example, the MFOLD program (Genetics Computer Group, Madison WI) and testing in vitro or in vivo as is known in the art. _Another useful method for identifying effective antisense compositions uses combinatorial arrays of oligonucleotides (see, *e.g.*, Milner *et al.*, 1997, Nature Biotechnology 15: 537). _Examples of oligonucleotides that can be tested in cells for antisense suppression of CLASP-5 function are those capable of hybridizing to (*i.e.*, substantially complementary to) CLASP-5 at the following positions:

Oligo	Sequence 5'- 3'	length	notes/comments
1	GATGTTGGAGCAGTAT CAGCATTCATA (SEQ ID NO:120)	27-mer	spans nucleotides 6-32 of the sequence of FIG. 1 (nucleotides 3087 to 3113 in FIG. 6)
2	GGGCAGCAGCCAGTTC TGTGAAGAGGAG (SEQ ID NO:121)	28-mer	spans nucleotides 154-181 of the sequence of FIG. 1 (nucleotides 3232 to 3259 in FIG. 6), and is complementary to the region encoding the cadherin EC motif
3	CAGCGGCGTGCACCA GGCACATGGCAGCC (SEQ ID NO:122)	29-mer	spans nucleotides 1650-1678 of the sequence of FIG. 1 (nucleotides 4728 to 4756 in FIG. 6), and is complementary to the region encoding the transmembrane domain

Paragraph beginning at line 4 of page 53 has been amended as follows:

The antisense nucleic acids (DNA, RNA, modified, analogues, and the like) can be made using any suitable method for producing a nucleic acid, such as the chemical synthesis and recombinant methods disclosed herein. In one embodiment, for example, antisense RNA molecules of the invention can be prepared by de novo chemical synthesis or by cloning. For example, an antisense RNA that hybridizes to CLASP-5 mRNA can be made by inserting (ligating) an CLASP-5 DNA sequence (*e.g.*, SEQ ID NO:1 ~~SEQUENCE ID No: 1~~, or fragment thereof) in reverse orientation operably linked to a promoter in a vector (*e.g.*, plasmid). Provided that the promoter and, preferably termination and polyadenylation signals, are properly positioned, the strand of the inserted sequence corresponding to the noncoding strand will be transcribed and act as an antisense oligonucleotide of the invention. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter or enhancer) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

Paragraph (Primer Table) beginning at line 20 of page 107 has been amended as follows:

Primer Table

CLASP gene	Sense Primer	Sense sequence	Sense SEQ ID NO:	Antisense Primer	Antisense sequence	Antisense SEQ ID NO:
CLASP-7	HC7gS5	AGGCCTTGTCTCTGTTTA CCTG	123	HC7gAS1	TGTCATGTACTGCACTCGCA CAGC	124
CLASP-7	HC7gS3	ACAGGAACCTGCTGTAC GTGTAC	125	HC7AS14	TCGTGGCTGCACAGGATGCG GGTG	126
CLASP-4	C4P2	GACCCATTAGGAGGTCT AC	127	HC4AS3'	CGGGATCCATTGTCACCGTA CATCTGC	128
CLASP-4	C4P2	GACCCATTAGGAGGTCT AC	127	HC4AS3'	CGGGATCCATTGTCACCGTA CATCTGC	128
CLASP-1	hC1S5'	TATGTCTCAGTCACCTAC CTG	129	HC1AS3'Kpn	CTTGGTACCACTTCAGCACT AGATGAGATG	130
CLASP-1	C1S7	TCAAGACCAGGGCATGC AAG	131	HC1AS3'Kpn	CTTGGTACCACTTCAGCACT AGATGAGATG	130

Paragraph beginning at line 1 of page 108 has been amended as follows:

In-frame stop codons were not present suggesting that the cDNA was not full length. To obtain the 5' terminus of CLASP-5, 5' RACE was employed. Antisense oligonucleotides directed against the 5' end of the longest CLASP-5 sequence were generated:

Primers used for human CLASP-5 5' RACE

Primer sequence(5' to ~~TO~~ 3') nucleotide position

HC5RACE2 (SEQ ID NO:133)

TGCTAGCATCTTCTCCACACATAAACTGG 1554 to 1582

HC5RACE3 (SEQ ID NO:134)

AGGTGGTTGTCCTGGGTGTGTACAGAAG 1997 to 2012